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# Hybrid material from Zn[aminoacid]$_2$ applied in the thio-Michael synthesis

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ABSTRACT

Recently, methodologies that are in accordance with green chemistry principles have been garnering increasing attention. One of the most applied methods in this field is heterogeneous catalysis. In this context, many catalysts have been developed, and there is one remarkable class that has emerged: hybrid materials. Such heterogeneous catalysts are developed from organic and inorganic portions, especially from amino acids and metal salts, which are commonly found in the literature. Herein, we introduce Zn[Pro]$_2$ and Zn[Gly]$_2$ as heterogeneous catalysts in thio-Michael reactions via the implementation of two methods: via (1) a magnetic stirrer and (2) via an ultrasound device; the latter method resulted in minimally increased reaction yields in all cases.

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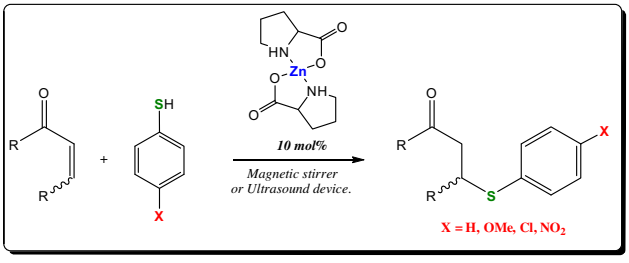
## Introduction

Thio-Michael is one of the most important reactions when the aim is to form a C–S bond. This reaction is responsible for many compounds described in the literature that have biological applications, such as antibiotics, antimicrobials, analgesics, and HIV medicines.[1] The compound most cited in the literature is diltiazem, a calcium channel blocker.[2] Many inorganic catalysts (Lewis acids) have already been reported, including $InBr_3$[3] and $Cu(BF_4)_2 \times H_2O$.[4] There are also other examples of organic catalysts applied specifically in the thio-Michael reaction. The most used one in this purpose is L-proline and, in a few cases, amino acids[5] although some researchers already have reported other catalysts from chalcone[6] and thiourea derivatives[7] applied in Michael or thio-Michael reactions.

However, thio-Michael reactions sometimes present shortcomings, such as long reaction times, high temperatures, expensive catalysts, and environmentally detrimental effects due to the use of catalysts that often cannot be recycled and may be made up of toxic metals.[8] For this reason, new procedures that provide compounds containing C–S bonds, which minimize the damage to the environment, have recently become increasingly desirable. In this environmental context, ultrasounds are being employed to minimize or even eliminate the presence of toxic by-products. There are many papers in the literature that report ultrasound use in organic reactions. As reported, it increases yields and decreases the reaction time in comparison to classical methodologies. Another methodological strategy to make such reactions more environmentally sound is heterogeneous catalysis. A heterogeneous catalyst that has been recently reported and is standing out in the literature is bis[prolinate-N,O]Zn or Zn[Pro]$_2$. Zn[Pro]$_2$ was used in a number of organic reactions such as the Mannich[9], aldol[10], and Hantzsch.[11] Considering this, we aimed to insert Zn[Pro]$_2$ as a heterogeneous catalyst in a thio-Michael reaction using the ultrasound method (Scheme 1). In addition, we aimed to similarly insert another heterogeneous catalyst from an amino acid complex, bis[glycinate-N,O]Zn or Zn[Gly]$_2$.




**Scheme 1.** General thio-Michael using Zn[Pro]$_2$ as catalyst.

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## Results and discussion

To prove our hypothesis and assess the catalytic ability of $Zn[Pro]_2$, we carried out the synthesis of the thio-Michael adduct from cinnamaldehyde and thiophenol, using this synthesis as the model reaction. A blank reaction (without $Zn[Pro]_2$) was carried out using equivalent molar amounts of cinnamaldehyde and thiophenol in a magnetic stirrer for 60 min. Three other reactions were carried out for comparison. The first used the same amounts of reagents as the blank reaction but also included 10 mol % $Zn[Pro]_2$. The second reaction differed from the blank reaction in that the reaction flask was inserted into the ultrasound device. Finally, in the last reaction, 10 mol % $Zn[Pro]_2$ was used in combination with the insertion of the reaction flask in the ultrasound device. All the reactions were carried out for 1 h. Data are presented in Figure 1.

The compound obtained from the reaction with cinnamaldehyde was reduced using $NaBH_4$ as the alcohol is more stable than the aldehyde.

As observed in Figure 1, when we concurrently used the ultrasound device and 10 mol % of the catalyst, we obtained the thio-Michael adduct in 80% in 1 h. It is worth noting that when using a chiral hybrid catalyst, $Zn[L\text{-}Pro]_2$, a dextro thio-Michael adduct was obtained. This result is important and contrary to the results from porcine pancreatic lipase.[12]

We expanded our methodology using other types of α,β-unsaturated carbonyl compounds as described in Table 1. As expected, the presence of the ultrasound device resulted in an improved process by decreasing the reaction time (entries 1–2 and 3–4) and increasing the yields by 12.4%, 16.7%, and 40.0% for the reactions involving chalcone, cyclohex-2-enone, and 3-methyl-cyclohex-3-enone, respectively.

The reaction using isophorone did not produce the thio-Michael adduct, and to the best of our knowledge, we attributed this effect to the presence of dimethyl groups bonded to carbon 5, which made it impossible for a nucleophilic attack to occur in the transition state following the reaction between $Zn[Pro]_2$ and isophorone. This fact was proven by data for 3-methyl-cyclohexen-2-one, which also presented a hindered effect but in the C3 position. For this compound, yields were lower when compared to the other Michael acceptor. Considering all results, we proposed a mechanism involving the cyclohexen-2-one and thiophenol (Fig. 2).

Aiming to expand the protocol described here, we used 4′-substituted thiophenol in the thio-Michael reaction using cyclohexen-2-one, and the resulting data are presented in Figure 3.

We also decided to use another hybrid heterogenic catalyst, bis[glycinate-N,O]Zn or $Zn[Gly]_2$, in the same reaction previously executed for $Zn[Pro]_2$; the resulting data are presented in Table 2. Two unexpected and important facts were observed in the

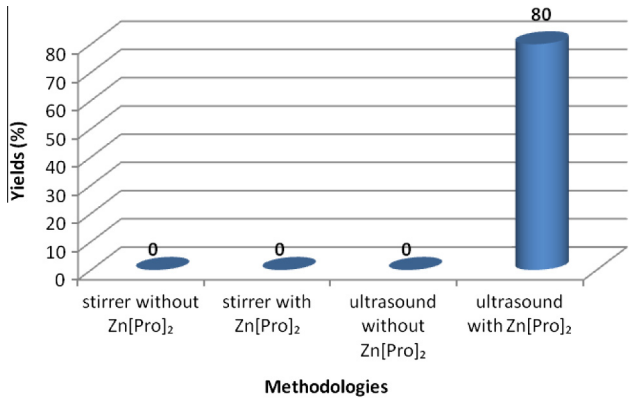


**Figure 1.** Yields obtained for the reaction using magnetic stirrer or ultrasound with and without $Zn[Pro]_2$.

**Table 1**
Protocol, Michael acceptor, solvent, and yields (%) for the thio-Michael reaction using the $Zn[Pro]_2$ as catalyst (10 mol %) and thiophenol

| Entry | Methodology | Michael acceptor | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | US | Chalcone | 5 | 89 |
| 2 | Stirrer | Chalcone | 10 | 85 |
| 3 | US | Cyclohex-2-enone | 15 | 96 |
| 4 | Stirrer | Cyclohex-2-enone | 60 | 80 |
| 5 | US | 3-Methyl-Cyclohex-3-enone | 60 | 50 |
| 6 | Stirrer | 3-Methyl-Cyclohex-3-enone | 60 | 30 |
| 7 | US | Isophorone | 60 | 0 |
| 8 | Stirrer | Isophorone | 60 | 0 |

[a] Yields obtained after purification by chromatographic column.

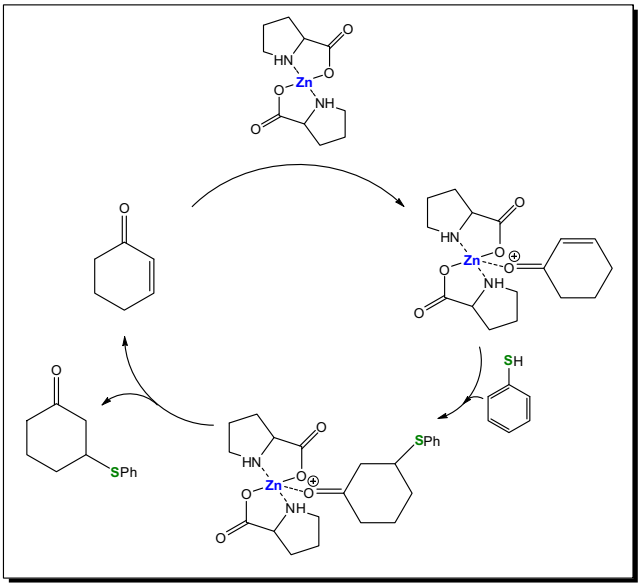


**Figure 2.** Plausible mechanism for Zn $[Pro]_2$ catalyzed the thio-Michael reaction.

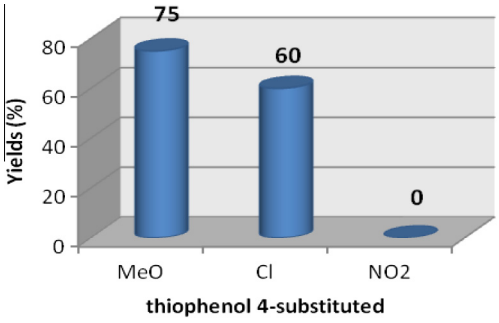


**Figure 3.** Yields obtained or the reaction involving cyclohexen-2-one and some 4-substituted thiophenols.

reactions with $Zn[Gly]_2$ when compared to $Zn[Pro]_2$: the increase in some reaction times (entries 1 and 3) and the decrease in the yields (Tables 1 and 2). Both facts can be explained by the dissolution of the catalyst $Zn[Gly]_2$ in the solvent media, which did not occur with $Zn[Pro]_2$. This shows that the process of purification for the reactions using $Zn[Gly]_2$ was more complex.

Finally, we carried out the reaction involving cyclohexanone and 4′-substituted thiophenol (4-OMe, 4-Cl, and 4-$NO_2$) testing the methodology with and without the ultrasound device and using $Zn[Gly]_2$ as catalyst. As observed for all the reactions

**Table 2**
Procedure (ultrasound and magnetic stirrer), Michael acceptors, solvents, reaction time (min), yields (%) for the thio-Michael reaction by applying $Zn[Gly]_2$ and thiophenol

| Entry | Michael acceptors | Solvent | Time[a] (min) | U.S. yield[b] (%) | Stirrer yield[c] (%) |
|---|---|---|---|---|---|
| 1 | Chalcone | $CHCl_3$ | 60 | 75 | 70 |
| 2 | Cinnamaldehyde[d] | EtOH | 60 | 70 | 65 |
| 3 | Cyclohex-2-enone | EtOH | 60 | 74 | 63 |
| 4 | 3-Methyl-Cyclohex-3-enone | EtOH | 60 | 40 | 34 |
| 5 | Isophorone | EtOH | 60 | 0 | 0 |

[a] Both procedures were performed using the same duration.
[b] Yields obtained using ultrasound device and after purification by chromatographic column.
[c] Yields obtained using magnetic stirrer and after purification by chromatographic column.
[d] Compound obtained for the reaction involving cinnamaldehyde was the corresponding alcohol.

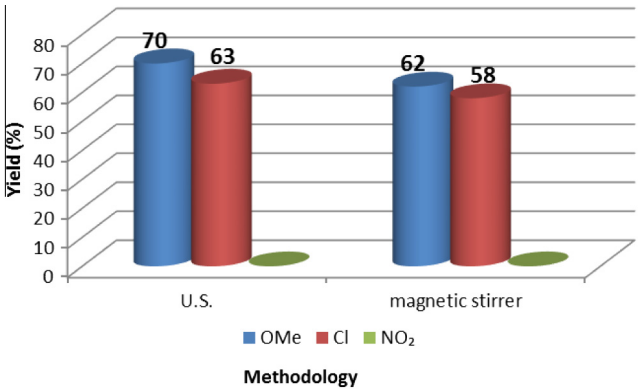


**Figure 4.** Yields obtained for the thio-Michael reaction involving thiophenols 4-substituted.

previously presented, the effect of the ultrasound device was very low in thio-Michael reactions involving 4′-substituted thiophenol (Fig. 4). Moreover, it was not possible to observe a significant effect for the reactions involving donor groups (MeO-groups) and weak withdrawing groups (chloro derivatives). The sole exception was during the use of a strong electron withdrawing group (nitro derivatives), with which we did not obtain the thio-Michael adduct, even with the use of an ultrasound device.

## Conclusion

We concluded that both hybrid heterogenic catalysts $Zn[Pro]_2$ and $Zn[Gly]_2$ furnished the thio-Michael adducts, except for isophorone, which is a much hindered ketone. In addition, with the modifications in the reactions' methodologies (magnetic stirrer and ultrasound device) the catalysts were efficient and provided the expected acceleration in the thio-Michael reaction. However, the use of the ultrasound device did not result in a substantial increase in the yields for thio-Michael adducts. Thus, we have shown herein the effectiveness of $Zn[Pro]_2$ and $Zn[Gly]_2$ as catalysts in thio-Michael reactions.

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## Supplementary data

Supplementary data (general experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.078.

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